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Unprecedented copper-catalyzed asymmetric conjugate addition of organometallic reagents to α,β-unsaturated lactams†

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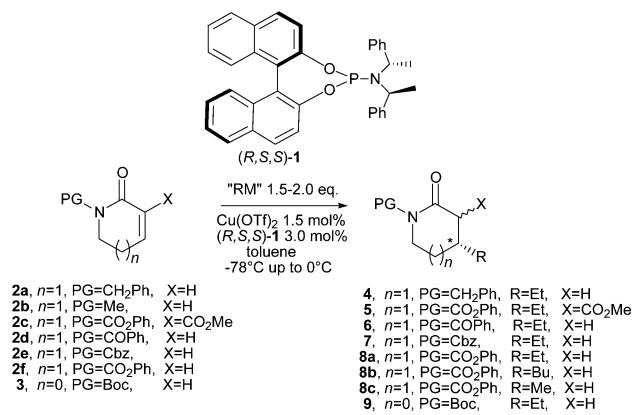
For the first time, an excellent enantioselectivity has been obtained in the conjugate addition of hard organometallic reagents to α,β-unsaturated lactams bearing appropriate protecting–activating groups on the nitrogen.

The asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most useful methods to assemble carbon–carbon bonds in organic chemistry, and several highly enantioselective processes have been developed.[1] In the case of α,β-unsaturated lactams, Hayashi has recently described a highly enantioselective Rh(I)/BINAP catalyzed 1,4-addition of arylboronic reagents to cyclic 5,6-dihydro-2(1*H*)-pyridinones.[2] Using a different approach, Buchwald very recently developed a catalytic enantioselective conjugate reduction of five- and six-membered α,β-unsaturated lactams.[3] However, the stereoselective introduction of a carbon–carbon bond in the β-position of a lactam is mostly based on the use of stoichiometric amounts of chiral auxiliaries[4] or reagents.[5] Chiral copper complexes with non-racemic BINOL-based phosphoramidites have proved to be excellent catalysts for the conjugate addition of dialkylzinc reagents to enones.[6] To the best of our knowledge, the catalytic enantioselective 1,4-addition of hard alkyl metals to α,β-unsaturated lactams has not been described. Here we wish to report an unprecedented enantioselective copper-phosphoramidite catalyzed alkylation of α,β-unsaturated lactams with dialkylzincs and trialkylaluminium reagents.

It is known that *N*-alkyl-α,β-unsaturated lactams without an additional withdrawing group in the α-position possess an inherently low reactivity.[7] Consistent with this observation, we found that *N*-methyl- and *N*-benzyl-5,6-dihydro-2(1*H*)-pyridinones **2a** and **2b** do not react with Et_2Zn in the presence of catalytic amounts of $Cu(OTf)_2$/(*R*,*S*,*S*)-**1** (Scheme 1).[8]

The contemporary introduction of a carbomethoxy group in the α-position and a carbamate protecting group for the nitrogen, as in compound **2c**, was able to overcome this low reactivity. In this case a very fast reaction occurred at −78 °C even in the absence of the catalyst and invariably the racemic *trans* adduct **5** was obtained as the major product. To minimize the uncatalyzed background reaction, the sole use of a protecting–activating group for the nitrogen proved to be sufficient (Table 1).



Scheme 1

The Cu(II)/(*R*,*S*,*S*)-**1** catalysed addition of Et_2Zn to the *N*-benzoyl lactam **2d** gave 83% conversion in 4 h from −78 °C up to 0 °C and 4-ethyl-2-piperidinone **6** was obtained with 26% ee (entry 1, Table 1). The Cbz-protected lactam **2e** underwent a clean addition reaction, with a complete conversion in 3 h from −78 °C up to 0 °C, to provide the corresponding β-ethyl substituted lactam **7** with 75% ee (entry 2).

During the search for a more enantioselective reaction, the *N*-carbophenoxy group was found to be superior to all the other protecting–activating groups in terms of both reactivity and enantioselectivity. Indeed substrate **2f** gave the corresponding β-ethyl substituted lactam **8a** with 95% ee and complete conversion in 2 h (entry 3). Similarly, the reaction of **2f** with Bu_2Zn was completed in 4 h from −78° to 0 °C and afforded the corresponding β-butylated lactam **8b** with a high ee (entry 4). Unfortunately, the easily accessible *N*-Boc-dihydropyrrol-2-one[10] **3** gave a more complex reaction mixture with dialkylzinc reagents and the corresponding β-ethylated addition product **9** was found to be not entirely stable under standard chromatographic purification on SiO_2 (entry 5).[11] δ-Lactams **2d–f** and *N*-Boc-γ-lactam **3** were not alkylated by Me_2Zn under our reaction protocol even using prolonged reaction times and a large excess of the reagent (data not shown in Table 1). Therefore, we decided to change the primary organometallic reagent from the poorly reactive Me_2Zn to Me_3Al in order to address the asymmetric formation of β-methylated lactams.

Trialkylaluminiums are interesting organometallic reagents because they are produced on an industrial scale and possess a high chemoselectivity and a low toxicity.[12] Only a few examples of enantioselective conjugate additions using trialkylaluminium reagents have been reported,[13] and to the best of our knowledge,

Table 1 Enantioselective conjugate addition of organometallic reagents ("RM") to α,β-unsaturated lactams catalysed by (*R*,*S*,*S*)-**1**/$Cu(OTf)_2$[a]

Entry	Lactam	"RM"	Time/*T*	Conv.[b]	Ee (%)[c]
1	**2d**	Et_2Zn	4 h/up to 0 °C	83 (50)	26
2	**2e**	Et_2Zn	3 h/up to 0 °C	100 (70)	75
3	**2f**	Et_2Zn	2 h/up to −50 °C	100 (65)	**95**
4	**2f**	Bu_2Zn	4 h/up to 0 °C	100 (52)	> 90[d]
5	**3**	Et_2Zn	4 h/up to 0 °C	90 (15)	35
6	**2f**	Me_3Al	2 h/up to 0 °C	100 (78)	68
7	**2f**	Et_3Al	1 h/up to −30 °C	100 (88)	28
8	**3**	Et_3Al	2 h/up to 0 °C	95 (25)[e]	3

[a] *Conditions*: all reactions were run in accordance with the typical procedure.[9] [b] Conversions are determined by ^1H NMR examination of the crude reaction mixture. Isolated yields after chromatographic purification (SiO_2) are reported in parentheses. [c] Determined by HPLC on Daicel Chiralcel OB-H or OD-H columns. [d] Determined after zinc enolate trapping with acetaldehyde. [e] Isolated yield after transformation into the corresponding *N*-benzyl derivative.[11]

† Electronic supplementary information (ESI) available: experimental procedures, enantioselectivity determinations and characterization data for all new compounds. See http://www.rsc.org/suppdata/cc/b4/b403793f/

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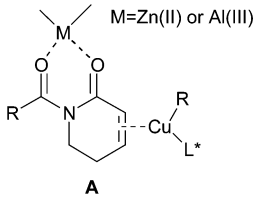
unsaturated lactams have never been used as substrates for this reaction. The $Cu(OTf)_2$–**1** catalysed addition of Me_3Al to lactam **2f** proceeded very cleanly in 2 h to give the corresponding methylated addition product **8c**, with a good enantioselectivity of 68% (entry 6). When the reaction was carried out with Et_3Al it was possible to obtain compound **8a** with a high yield, albeit with a modest 28% ee (entry 7). Also with the γ-lactam **3**, the use of Et_3Al proved to be less enantioselective than Et_2Zn (entry 8).

It is reasonable to assume that the different reactivity displayed by *N*-alkyl- and *N*-carbonyl-δ-lactams with dialkylzinc and organoaluminium reagents is due to the greater electron withdrawing ability of the latter protecting–activating group, which renders the reactive β-carbon more electrophilic in nature. Furthermore, a chelation by the metal ions of the two carbonyl oxygens, as shown in **A** (Fig. 1), might be responsible for a further double bond activation[14] and for a beneficial reduction of the conformational mobility of the substrate.

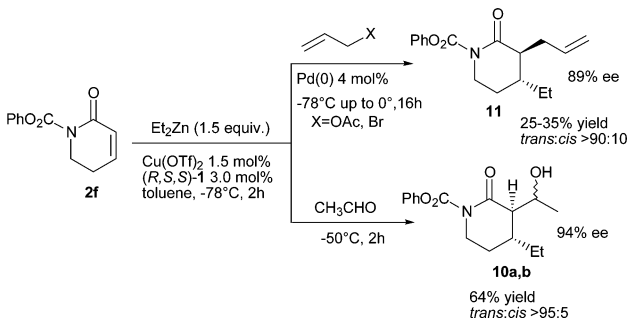


A

Fig. 1 Plausible intermediate metal-chelated structure.

Conjugate addition to unsaturated ketones, followed by trapping of the zinc enolate with an electrophile, is an efficient method to build up more complex molecules.[15] Here we report that also the intermediate zinc enolate derived from the conjugate addition of Et_2Zn to unsaturated lactam **2f** can be trapped with acetaldehyde at −50 °C to give the new *trans*-3,4-disubstituted 2-piperidinone **10a,b** as an inseparable mixture of aldols with 94% ee (Scheme 2).[16] Furthermore, the same intermediate can be trapped in a one-pot procedure by allyl bromide or allyl acetate and 4 mol% of $Pd(PPh_3)_4$ to deliver piperidinone **11** with 89% ee, albeit with 25–35% isolated yield.[17] It should be noted that substituted six-membered lactams can also serve as precursors to enantiomerically enriched piperidines which are important structural motifs in pharmaceuticals.[18]

In conclusion, we have reported the first catalytic asymmetric alkylation of α,β-unsaturated lactams with hard organometallic reagents. The reaction gives access to new β-alkyl-substituted δ-lactams in an enantioenriched form. Further findings established that the reaction is also amenable to three-component processes to give α,β-disubstituted lactams.



Scheme 2

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8 A useful conversion of compounds **2a** can only be obtained by the use of THF as the reaction solvent (see Supporting Information). However, the corresponding adduct **4** was obtained as a racemate.

9 *Typical procedure*: a solution of $Cu(OTf)_2$ (2.5 mg, 0.0069 mmol) and (*R*,*S*,*S*)-**1** (7.5 mg, 0.00138 mmol) in anhydrous toluene (1 ml) was stirred at room temperature for 40 min. The colorless solution was cooled to −78 °C and subsequently a solution of the lactam (0.46 mmol) in the minimal amount of toluene (or CH_2Cl_2 for **2f**) and 0.69 mmol of R_2Zn or R_3Al (0.92 mmol) were added. The reaction was followed by TLC analysis and quenched with saturated aqueous NH_4Cl after the times and at the temperatures indicated in Table 1.

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